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Supplementary webappendix

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Supplementary information

Spread of Yellow Fever Virus outbreak in Angola and the Democratic Republic Congo 2015-2016: a modelling study

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Calculation of the generation time distribution of yellow fever

Although epidemiological parameters of yellow fever are still poorly characterised, we can try to use field and experimental data to reconstruct the generation time distribution of yellow fever.

Human incubation period (HI)

The incubation period is the time between infection and the time of symptom onset. For the human incubation period we used a truncated exponential distribution with a mean of 4 days and a maximum time of one week.[1]

Human to mosquito transmission (HM)

We assume that the duration of infectivity of human cases is exponentially distributed with a mean of 3 days for up to a maximum of 10 days.[2]

Mosquito infectiousness (MI)

The period of mosquito infectiousness depends on the lifespan of the mosquito and the extrinsic incubation period (the time between infection in the mosquito from blood feeding of an infectious human to it becoming infectious itself and able to transmit to a new host). The average lifespan of *Aedes aegypti* is 7 days with a maximum of 30 days.[3] The extrinsic incubation period for yellow fever has been estimated at 6·9 days.[2]

Generation time distribution

We derived the empirical distribution of the generation time by simulating values for HI, HM and MI. A human case contributed to the transmission process on each day they were infectious (so the number of mosquitoes infected by a case was proportional to the duration of infectivity of the case). The same was true for mosquitoes.

Figure S1 shows the empirical generation time distribution we obtained. The generation time is estimated to have a mean of 15·0 days and a standard deviation of 5·6 days.

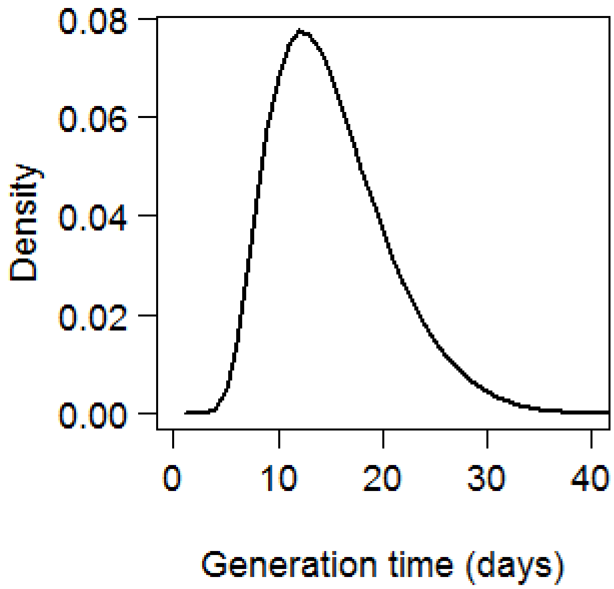


Figure S1: Empirical distribution of the generation time for Yellow Fever.

Estimation of the exponential growth rate, the doubling time and the reproduction number

Exponential growth rate

We fit a simple exponential growth rate model to the early stage of the epidemic:

$$I_w = I_0 exp(r_W . w)$$

where I_w is the number of cases on week w.

The time period for which exponential growth occurs is determined by plotting the log of the weekly number of cases (Figure S1) and selecting the time period when this variable grows linearly. A simple linear model is then fitted on this time period to estimate r_W:

$$ln(I_w) = ln(I_0) + r_W . w$$

The daily exponential growth rate r is a simple function of the weekly exponential growth rate r_W:

$$r = r_W/7$$

Between week 1 and week 5 in 2016, we estimate that the weekly exponential growth rate r_W is 0·80 (95% CI: 0·71, 0·90) and the daily exponential growth rate r is 0·11 (95% CI: 0·10, 0·13).

Doubling time

The doubling time D can be derived from the exponential growth rate r with the following formula:

$$D = ln(2)/r$$

Reproduction number

Denote $g(.)$ the density of the generation time (i.e. time lag from the infection of a case to the infection of the persons they infect). The following formula can be used to derive the reproduction number R from the exponential growth rate r if the generation time distribution $g(.)$ is assumed to be known.[4]

$$R = \frac{1}{\int_0^\infty exp(-r.t)g(t)dt}$$

Human movement metrics:

Two generalized movement models used in this analysis were the gravity model $T_{i,j} = k\frac{N_i^\alpha N_j^\beta}{d_{i,j}^\gamma}$, and the radiation model $T_{i,j} = T_i \frac{N_i N_j}{(N_i+s_{i,j})(N_i+N_j+s_{i,j})}$, where total commuting is $T_{i,j}$ from district i, to j; N_i^α is the population in the origin and N_j^β in the destination district; $d_{i,j}^\gamma$ the distance between them, and $s_{i,j}$ the population in the radius between *i* and *j*.

Geographic spread model

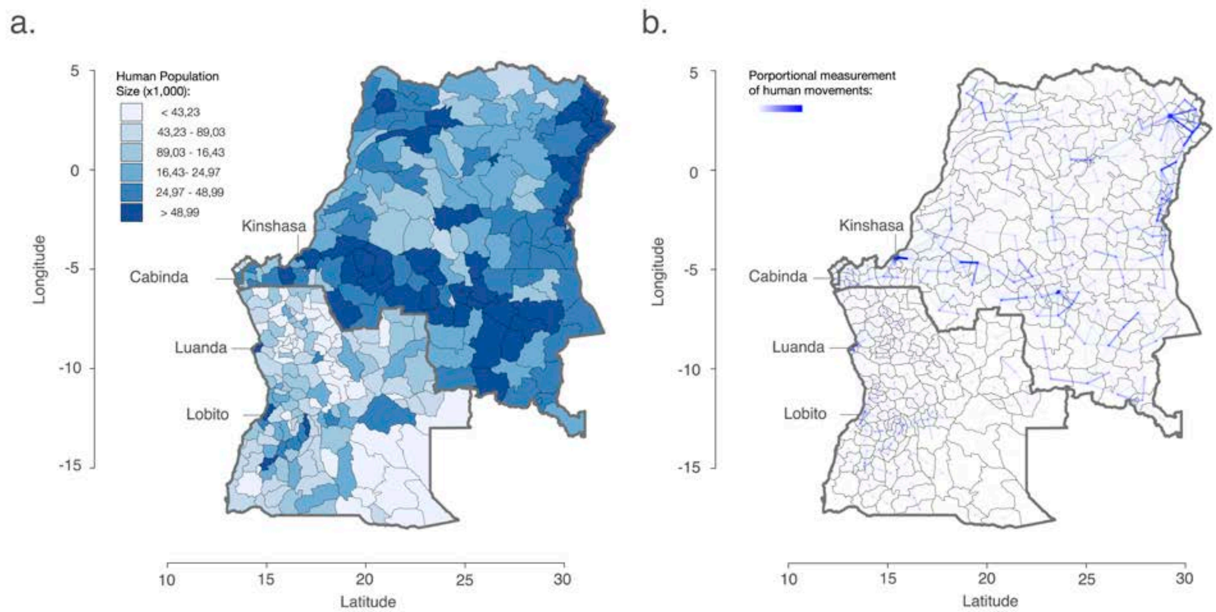


Figure S2: Population distribution in the study area (a) and relative human connectivity (b) between each district (Angola) and commune (DRC). The width of the arrows indicate the strengths of the connection.

Figure S3: Road network in Angola and southern Democratic Republic Congo (www.maps.google.com).

Table S1: List of variables used in geographic spread model.

	Name	Reference
1	Great circle distance	rdist.earth function in the 'fields' package in R
2	One away adjacency	GADM shapefile (http://www.gadm.org)
3	Two away adjacency	GADM shapefile (http://www.gadm.org)
4	Three away adjacency	GADM shapefile (http://www.gadm.org)
5	Gravity model	Movement package in R, based on Zipf et al. 1946[5]
6	Radiation model	Movement package in R, Simini et al. 2012[6]
7	Uniform selection model	Simini et al. 2013[7]
8	Binary variable pre/post expansion phase	Before and after week 14
9	*Aedes aegypti* suitability	Kraemer et al. 2015[8]
10	*Aedes aegypti* suitability weighted by mobility	Kraemer et al. 2015[8], Simini et al. 2012[6]
11	Travel time distance	Uchida and Nelson 2008[9]

Supplementary Results

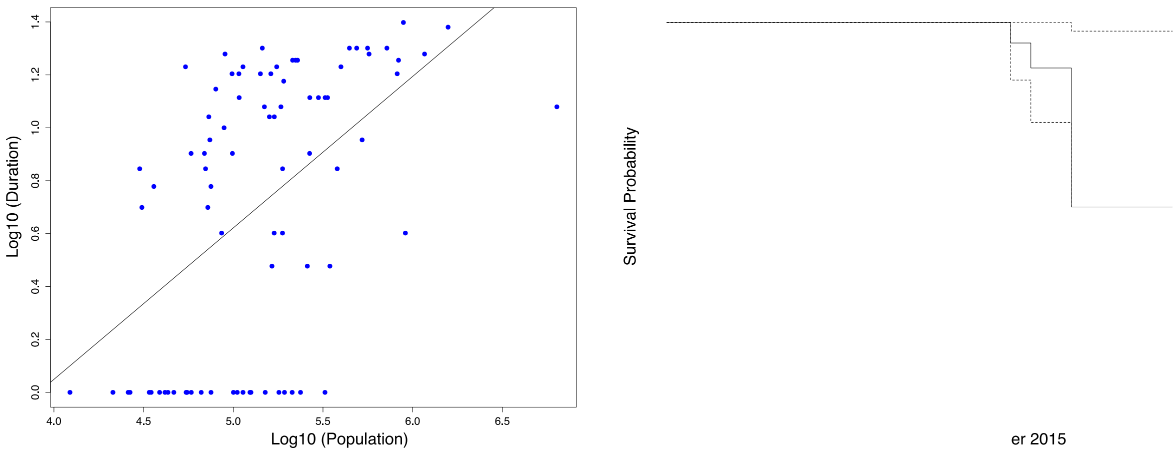


Figure S4: Results showing the relationship between population density and duration of transmission (a). Panel b) shows the results from the Cox model.

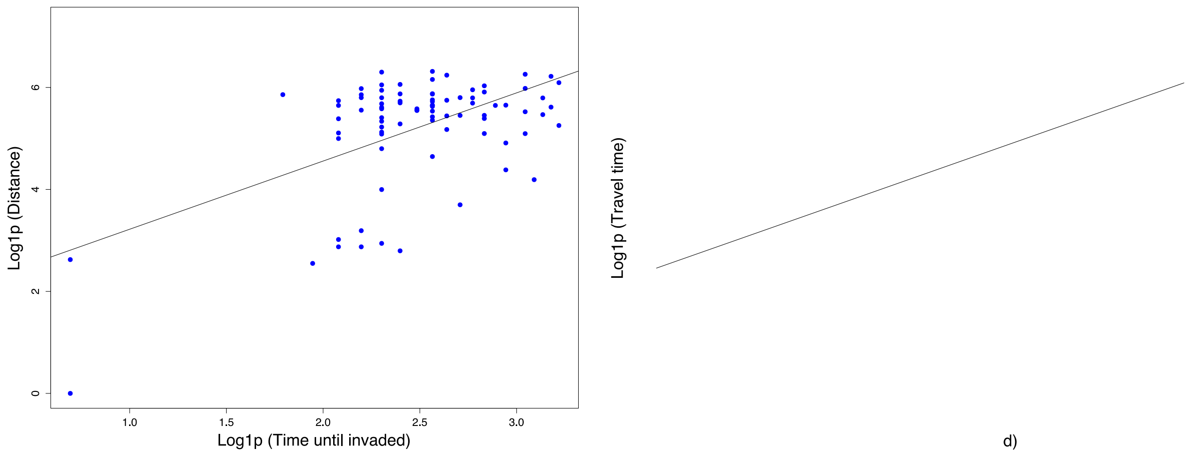
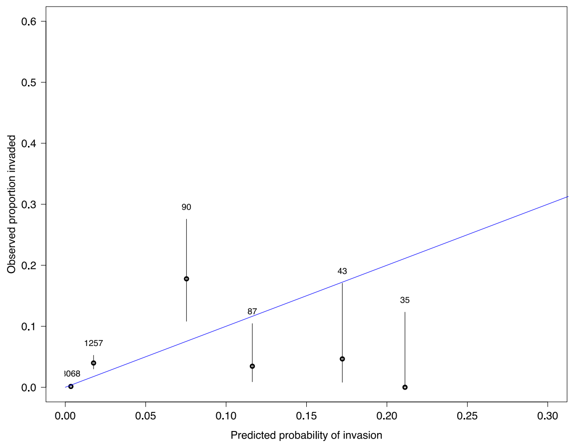


Figure S5: Relationship between distance (a), travel time (b) and time until a district was invaded.



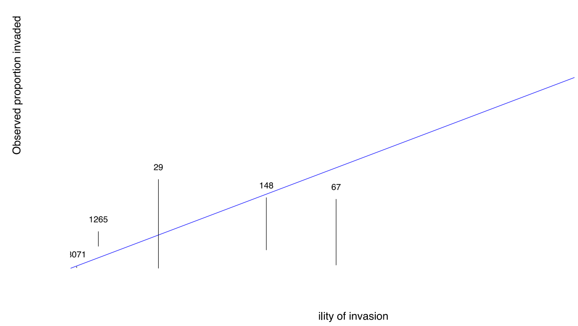


Figure S6: Comparison between observed proportion of districts invaded and their predicted probabilities using the univariate models; a) *Aedes aegypti* probability of occurrence; b) Great circle distance; c) Gravity metric; d) Neighborhood model; e) Radiation metric; f) Travel distance metric.

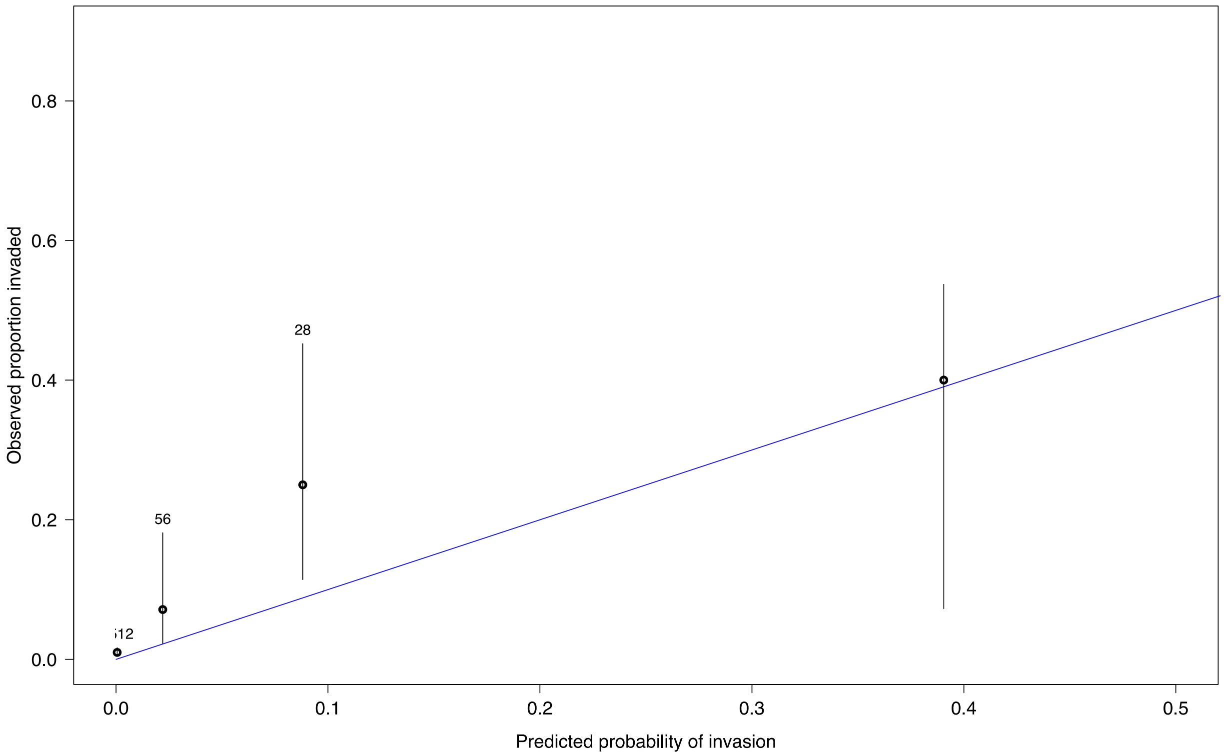


Figure S7: Model accuracy for the real-time predictions between weeks 9-12 of 2016 during the outbreak with a model using data only until week 8 of 2016. Blue line indicates perfect calibration.

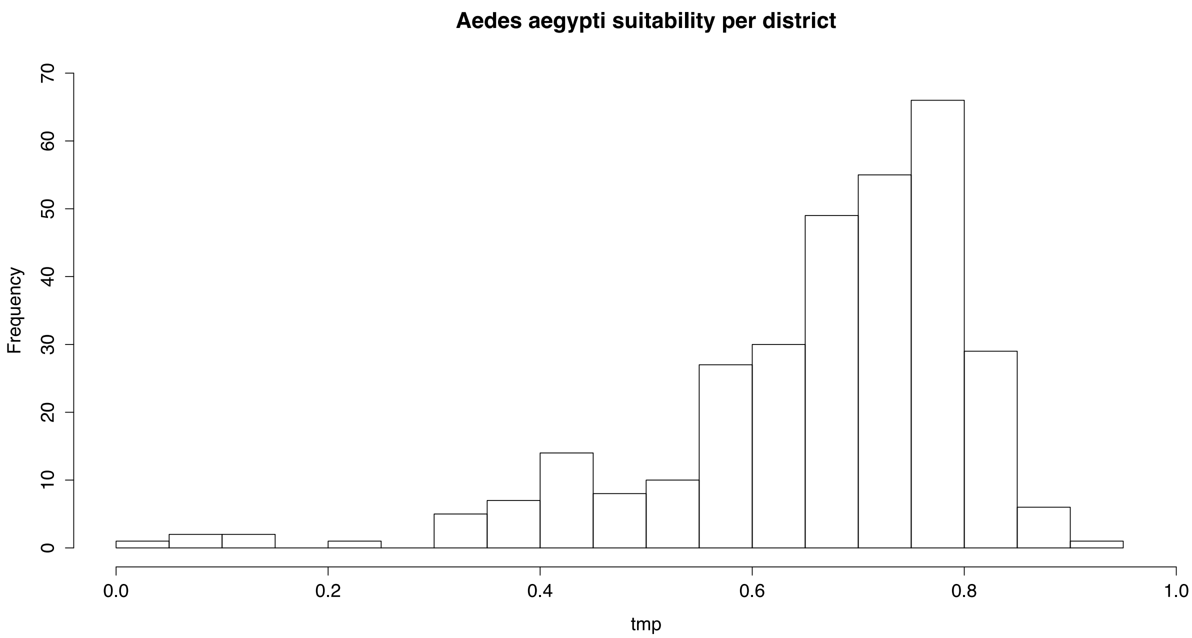


Figure S8: Histogram of district mean values of *Aedes aegypti* suitability for the study region. Estimates are taken from Kraemer et al. 2015.[8]

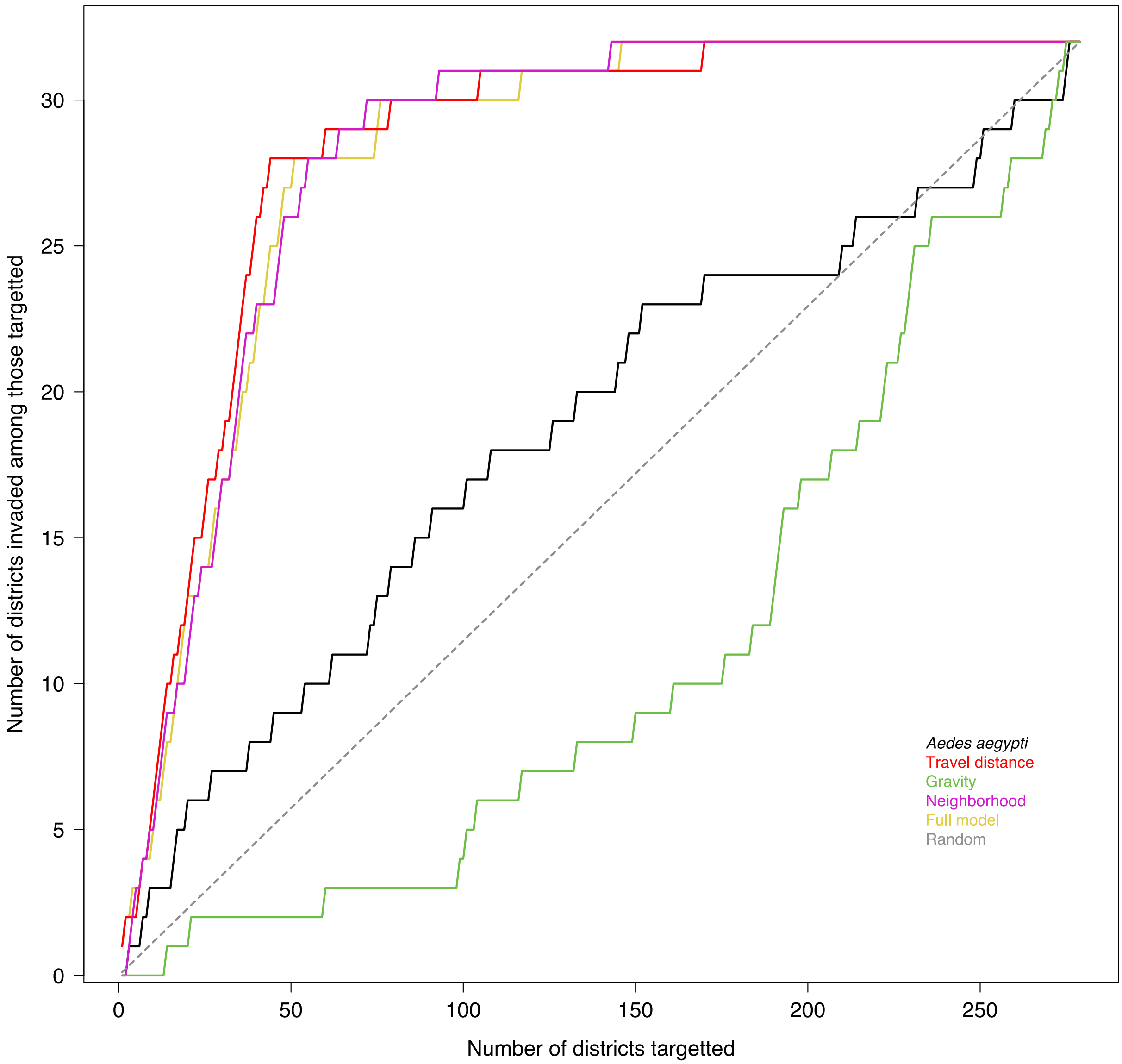


Figure S9: Model comparison of full model vs. univariate models for the expansion phase of the outbreak.

Table S2: Inclusion probability of variables in the model when using backward selection based on significance.

Name	Weeks variable was retained in the model (starting week 11 of outbreak)	Total number of weeks
Great circle distance	11, 18, 19, 21, 23, 25, 27 – 34	14
One away adjacency	14	1
Two away adjacency	15-34	20
Three away adjacency	13, 14, 16, 18	4
Gravity model	11-14, 16-18, 21-34	21
Radiation model	14, 15, 19-23, 25-34	17
Uniform selection model	11, 12, 21, 23-25, 27-34	14
Binary variable pre/post expansion phase	14-34	21
Aedes aegypti suitability	12, 13, 16-19, 21-24, 26-34	19
Aedes aegypti suitability weighted by mobility	13, 14, 16-18, 21-34	19
Travel time distance	12-17, 20	7

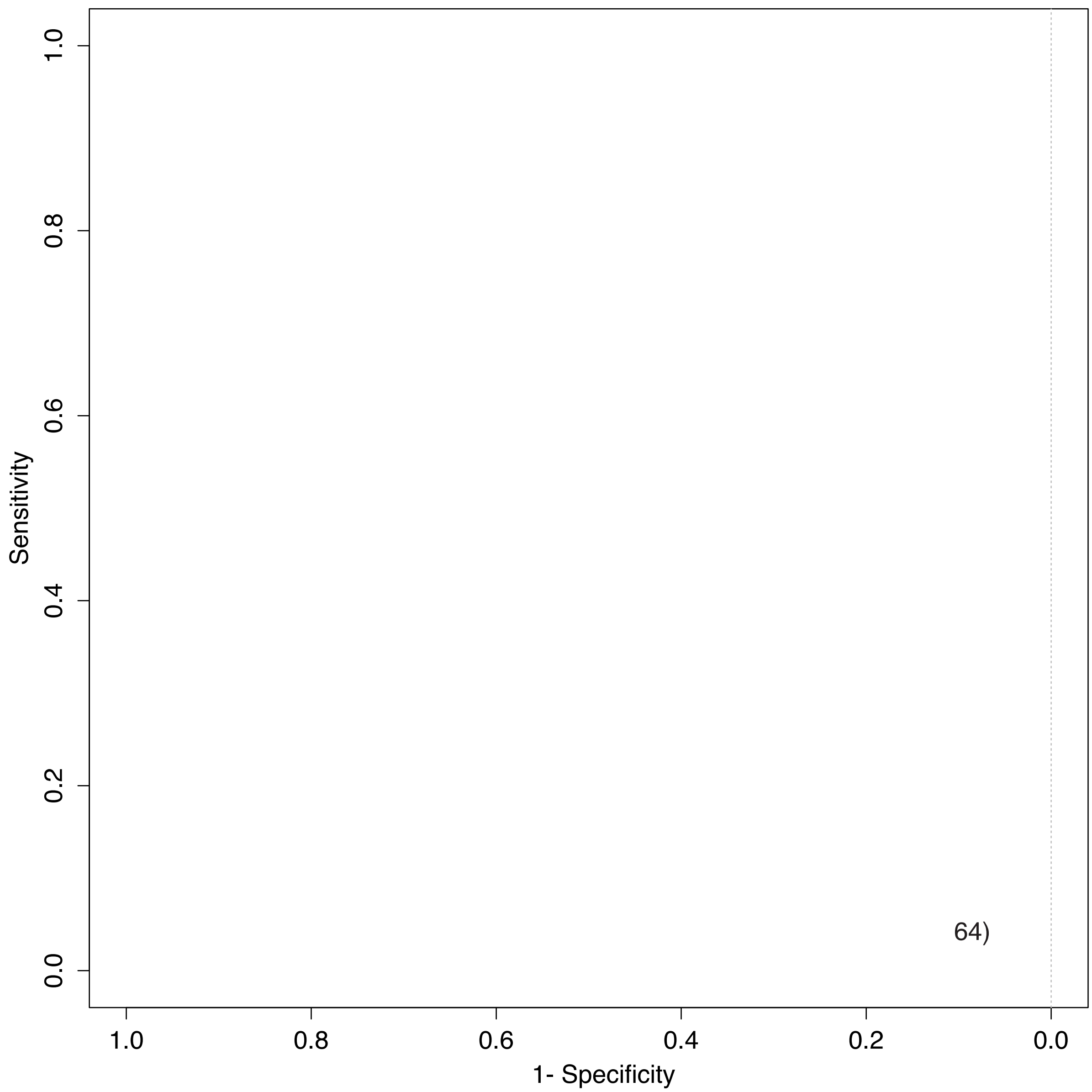


Figure S10: Predictive accuracy of the full model (green) and the full model assuming reporting delays (red) of four weeks in the early phase of the epidemic (until week 9 of 2016) and one week in subsequent weeks.

Table S3: Parameter coefficients for full model and full model assuming reporting delays of four weeks in the early phase of the epidemic (until week 9 of 2016) and one week delay in subsequent weeks.

Parametric coefficients	Covariate	Estimate	Ch.sq	Std. error	p-value
Full model	Intercept	-6.365271		0.411084	<0.001
	Three away	-0.098956		0.063441	<0.001
	Before/after intervention	-0.053673		0.007646	<0.001
	Aedes (smooth)		59.72		<0.001
	Radiation model (smooth)		33.33		<0.001
	Gravity model (smooth)		47.86		<0.001
Full model assuming reporting delays	Covariate	Estimate	Ch.sq	Std. error	p-value
	Intercept	-7.162161		0.690742	<0.001
	Three away	-0.069311		0.063506	<0.001
	Before/after intervention	0.051188		0.007419	<0.001
	Aedes (smooth)		66.73		<0.001
	Radiation model (smooth)		29.25		<0.001
	Gravity model (smooth)		40.48		<0.001

Table S4: Parameter coefficients for the full model with assumed delays of the effect of vaccination three weeks prior to implementation until five weeks after.

week of implementation	coefficient	p-value	Std error	Dev explained
-5	-0.03254	>0.05	0.05617	24.4%
-4	-0.03254	>0.05	0.01715	24.4%
-3	-0.08947	<0.001	0.01160	33.6%
-2	-0.08949	<0.001	0.01159	33.6%
-1	-0.068937	<0.001	0.008667	32%
0	-0.0537	<0.001	0.007195	30.8%
1	-0.03528	<0.001	0.005253	28.4%
2	-0.039253	<0.001	0.005377	30.1%
3	-0.040447	<0.001	0.005435	30.4%
4	-0.038561	<0.001	0.005214	30.3%
5	-0.042271	<0.001	0.005414	31.5%
6	-0.042866	<0.001	0.005569	31.7%

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